REMARKS

Claim 8 is pending in this application. Claim 8 has been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection Under 35 U.S.C. §103

Claim 8 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (1996) in view of Bard et al. (1977). The Advisory Action asserts that the rejection is based upon the combination of Yoshida et al. and Bard et al. as discussed in the prior action. The Yoshida et al. reference is suggested to teach a method of identifying an agent that increases oncogenic protein degradation comprising contacting a cell expressing PML/RARa with the anti-cancer agent ATRA and detecting whether ATRA increases PML/RARa degradation. It is suggested that the method of Yoshida et al. reads on instant claim 8 preamble and step ii (contacting a cell that expresses PML/RARa with an agent and detecting whether the agent increases PML/RARa protein degradation). The Office acknowledges that the reference is silent with regard to lysosomal destabilization and the section the Applicant references only states that, "The degradation of most cellular proteins is catalyzed by the non lysosomal ubiquitin-proteosome pathway, which is dependent upon ATP and closely involved in the proteolysis of aberrantly generated products." The Advisory Action asserts that one of ordinary skill in the art would certainly recognize that if lysosomes were destabilized by ATRA, the degradation of aberrant proteins would have to proceed by another route such as the non-lysosomal

ubiquitin-proteosomal pathway. The Office contends that Bard et al. teaches that it was known in the art at the time of the invention to contact cells with anticancer agents and detect whether the agents destabilize lysosomes as determined by the release of lysosomal proteins into the cytosol (Reading on claim 8 preamble and step i). It is concluded that it would have been obvious to one of ordinary skill in the art to combine the two methods for screening for properties of anticancer agents into a single method for performing the same purpose.

Applicants respectfully traverse this rejection. At the outset, Applicants respectfully point out that in the reply mailed July 20, 2010, Applicants directed the Office's attention to the entire paragraph spanning pages 2946-2947 of Yoshida et al. This paragraph states:

> Accordingly, we supposed that PML-RARA bound with ATRA might become unstable and undergo accelerated degradation. The degradation of most cellular proteins is catalyzed by the nonlysosomal ubiquitin-proteasome pathway, which is dependent on ATP and closely involved in the proteolysis of aberrantly generated products (13). To investigate whether proteasomes are involved in the decrease of PML-RARA by ATRA, we examined the effect of the *Streptomyces* metabolite lactacystin (14), a highly specific inhibitor of the proteasome (15). The decrease of PML-RARA induced by ATRA was dose-dependently inhibited by lactacystin (Fig. 4). Lactacystin at 10 μM almost completely inhibited the decrease of PML-RARA induced by 1 μM ATRA. These data suggest that ATRA accelerates the degradation of PML-RARA in the proteasome pathway.

Therefore, contrary to the Office's assertion that the cited passage only states that, "The degradation of most cellular proteins is catalyzed by the non lysosomal ubiquitin-proteosome pathway, which is dependent upon ATP and closely

involved in the proteolysis of aberrantly generated products," the cited passage specifically teaches that "ATRA accelerates the degradation of PML-RARA in the proteasome pathway." This is direct contrast to the instant invention, which is directed to the identification of agents that induce the lysosome-dependent degradative pathway (page 5, lines 1-26 of the instant Specification). Indeed, as described at page 5, lines 10-11, proteasome and caspase inhibitors do not block PML/RARα degradation in accordance with the instant assay. In this respect, the instant assay requires the identification of agents that both destabilize lysosomes and increase PML/RARα protein degradation.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

In the instant case, the whole of the teachings of Yoshida et al. show that PML/RARα is degraded via the proteasome pathway, *i.e.* a non-lysosomal pathway. Thus, Yoshida et al. unquestionably teach away from doing what Applicants have done; *i.e.*, determining whether an agent destabilizes lysosomes and increases lysomal-dependent PML/RARα protein degradation. Accordingly, there would be no motivation to further look to the teachings of Bard et al. for determining whether an agent destabilizes lysosomes.

Furthermore, while the Advisory Action asserts that one of ordinary skill in the art would certainly recognize that if lysosomes were destabilized by ATRA, the degradation of aberrant proteins would have to proceed by another route

such as the non-lysosomal ubiquitin-proteosomal pathway, Applicants respectfully assert that the teachings of Bard et al. cannot be considered as being pertinent to the teachings of Yoshida et al. Bard et al. teach that retinoids are toxic at higher than physiological concentrations because they destabilize membranes (see page 115, col. 1, para. 2). As shown in Figure 3 of Bard et al., the concentration of retinoid achieving this effect was between 2 and 20 μM. In contrast, Yoshida et al. teach the differentiation of APL cells using 1 μM ATRA, with no discussion of ATRA toxicity. Therefore, there would simply be no rationale for the skilled artisan to combine the assay of Yoshida et al., as it relates to the differentiation of APL cells, with the toxicity assay of Bard et al.

Accordingly, Applicants respectfully assert that the basis of this rejection is not supported by the whole of the teachings of the cited references. Thus, the combined teachings of Yoshida et al. and Bard et al. cannot be held to make the present invention obvious under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Advisory Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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